PATENT
Atty. Docket No.: 2021.0036

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,808,614)
)
Issued: February 28, 1989)
)
To: Larry W. HERTEL)
)
Assignee: Eli Lilly and Company)
)
For: DIFLUORO ANTIVIRALS AND)
INTERMEDIATE THEREFOR)

#17

ATTN: BOX PATENT EXT.
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PETITION FOR EXTENSION OF TIME

Applicant hereby petitions for a four-month extension of time to respond to the communication dated March 14, 1997. A check in the amount of $1,470.00 is enclosed for the requisite fee.

To the extent any extension of time under 37 C.F.R. §1.136 is required to obtain entry of this response, such extension is hereby requested. If there are any fees due under 37 C.F.R. § § 1.16 or 1.17 which are not enclosed, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
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Reg. No. 40,266

Date: August 14 1997

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1. Applicant is an intended beneficiary of the patent term restoration provisions of 35 U.S.C. § 156

Title 2 of the Drug Price Competition and Patent Term Restoration Act of 1984, codified in 35 U.S.C. § 156, permits extension of the patent term for patents directed to new drug products required to undergo pre-market regulatory review by the Food and Drug Administration. These review procedures are typically very expensive and time consuming.

The patent term restoration provisions of § 156 were adopted to provide an incentive for companies to undertake this costly and time consuming regulatory process, and to compensate, at least in part, the patent owner for patent term lost during the pre-market regulatory review. The provisions of § 156 were intended to "ameliorate the loss incurred when patent terms tick away while the patented product is awaiting regulatory approval for marketing...." *Unimed v. Quigg*, 888 F.2d 826, 829, 12 U.S.P.Q.2d 1644, 1647 (Fed. Cir. 1989).

The record shows that Eli Lilly and Company is both the owner of U.S. Patent 4,808,614, and the marketing applicant who spent more than nine years working with the Food and Drug Administration (FDA) before the product GEMZAR® was approved for commercial marketing pursuant to § 505 of the Federal Food, Drug, and Cosmetic Act on May 15, 1996.

Although the regulatory review process was started on January 28, 1987, more than two years prior to the grant of U.S. Patent 4,808,614, Eli Lilly and Company did not receive approval from the Food and Drug Administration for commercial marketing of

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GEMZAR® until May 15, 1996. The date of approval is more than seven years after the patent was issued on February 28, 1989.

Accordingly, Eli Lilly and Company has lost several years of effective patent term due to the time consuming and expensive procedures of pre-market regulatory review of GEMZAR®. Eli Lilly and Company has not only created and developed the product which has been approved by the FDA, but has made the huge investment in time and resources to ensure that the product can be marketed to the public in the United States in a safe and effective manner.

2. Active ingredient must be present in the drug product when administered

Under 35 U.S.C. § 156(a), a patent is eligible for term extension if several conditions are met. The sole issue that has been raised regarding the eligibility of U.S. Patent 4,808,614 for patent term extension relies on the requirement in paragraph (a) that a patent must claim a product, a method of using a product, or a method of manufacturing a product to be eligible for patent term extension under § 156. For the purposes of § 156, the term "product," as it relates to a drug product, is defined in § 156(f)(2) as follows:

> (2) The term 'drug product' means the active ingredient of-
> (A) A new drug, antibiotic, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act)...including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient

Although neither § 156 nor the PTO regulations implementing this statutory provision contain a definition of "active ingredient," the Food and Drug Administration

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has provided a definition of active ingredient for purposes of implementation of § 156 as follows:

> *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or of animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

21 C.F.R. § 60.3(b)(2).

Thus, an active ingredient for the purposes of patent term extension under § 156 is interpreted as being any component of the drug product which is intended to furnish pharmacological activity or a direct effect in the treatment of disease. The definition of "active ingredient" includes those components that may undergo a chemical change and be present in a modified form intended to furnish the specified activity or effect. For purposes of patent term extension, an active ingredient must be present in the drug product when administered. See *Glaxo Operations UK. Ltd. v. Quigg*, 706 F.Supp. 1224, 1227-28, 10 U.S.P.Q.2d 1100, 1103 (E.D.Va. 1989), aff'd, 894 F.2d 392, 13 U.S.P.Q.2d 1628 (Fed. Cir. 1990). Thus, an active ingredient may be any component of the drug product when administered that is intended to furnish pharmacological activity or have another direct effect as defined in 21 C.F.R. § 60.3(b)(2).

3. Gemcitabine is an active ingredient present in the drug product when administered

The new drug application submitted under § 505(b) of the Federal Food, Drug, and Cosmetic Act for GEMZAR® for injection was approved on May 15, 1996. See

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Exhibit XI of the patent term extension application. GEMZAR® is a new drug within the meaning of the Federal Food, Drug and Cosmetic Act and § 156(f)(2).

According to the product information sheet for GEMZAR® (Exhibit I of the patent term extension application), it is the hydrochloride salt of gemcitabine. It is a nucleoside analog that exhibits antitumor activity. According to the product information sheet, it is a white to off-white solid that is for intravenous use only.

As noted under the "Dosage and Administration" section of the product information sheet, GEMZAR® should be administered by intravenous infusion. The recommended diluent for reconstitution of GEMZAR® is 0.9% sodium chloride injection without preservatives. According to the recommended instructions for use, appropriate dilutions of GEMZAR® (the hydrochloride salt of gemcitabine) yield a gemcitabine concentration of 40 mg/ml. The appropriate amount of drug may be administered as prepared or further diluted to concentrations as low as 0.1 mg/ml.

GEMZAR® itself is not administered to the patient, but is authorized to be administered as a clear, colorless solution which contains up to 40 mg/mL of gemcitabine. Because the salt is dissolved in an appropriate pharmaceutically acceptable solvent for administration to a patient, an equilibrium is established in solution between the salt and gemcitabine. GEMZAR® is provided as the dry hydrochloride salt in order that the active ingredient, gemcitabine, may be solubilized when placed in solution. That is, once the dry form of GEMZAR® is contacted with water, 09.% sodium chloride solution, or some similar vehicle for IV administration,

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gemcitabine hydrochloride dissociates into, inter alia, gemcitabine, the compound specifically claimed in the '614 patent.

As noted in the product information sheet under the section entitled "Clinical Pharmacology," gemcitabine (present in the drug product as administered) exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis and also blocking the progression of cells through the G1/S-phase boundary. As further noted in that section, the cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis.

It is clear from the product information sheet that gemcitabine is a component of the drug product as administered by injection, and is intended to furnish not only pharmacological activity, but also a direct effect in the treatment of metastatic pancreatic cancer. (See the product information sheet under the heading entitled "Clinical Studies.") Accordingly, gemcitabine meets the definition of an active ingredient because it is intended to furnish the prescribed pharmacological activity and because it is a component of the drug product as administered.

Applicant acknowledges that the application for patent term extension identified gemcitabine hydrochloride, or the hydrochloride salt of gemcitabine, as the active ingredient in the product approved by the FDA as GEMZAR® For Injection. The application was prepared and filed prior to the decision of the Federal Circuit in *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*, 109 F.3d 756, 42 U.S.P.Q.2d 1220 (Fed. Cir. 1997). Nevertheless, for the reasons advanced in this request for

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reconsideration, the '614 Patent is considered to be eligible for patent term extension under § 156. This is the first opportunity that applicant has had to explain the eligibility of the '614 Patent for patent term extension following the Hoechst-Roussel decision of March 28, 1997.

4. U.S. Patent 4,808,614 claims gemcitabine--an active ingredient in the drug product when administered

As noted in the application for patent term extension, and particularly in paragraph 9 on pages 4-6, claims 1, 2, 7, 8, 11 and 12 of the patent claim gemcitabine. Gemcitabine is a compound that falls within the scope of each of these claims.

Applicant respectfully submits that gemcitabine is not only an ingredient, but an active ingredient in the drug product when it is administered to a patient. The '614 patent must be considered to "claim" an active ingredient in GEMZAR® as it is administered to a patient, and thereby meet the threshold eligibility criterion of § 156(a).

5. The decision in *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman* undermines the purposes of § 156 and is contrary to past PTO practice

It is not the purpose of this request for reconsideration to challenge the holding in the Hoechst-Roussel case. It is respectfully submitted, however, that the holding is contrary to past PTO practice in administering the patent term extension statute and will undermine the purposes and symmetry that Congress sought to establish by enacting § 156.

In implementing the provisions of Public Law No. 100-670, 102 Stat.3971 (November 16, 1988), which permits owners of patents relating to new animal drug or

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veterinary biological products that are not biotechnology-generated to apply for extension of the terms of such patents, the PTO reiterated its position that the 1984 Act was intended to restore to those patent owners a portion of the enforceable term of an appropriate patent of their choice which was lost due to Government required regulatory review for the product covered by the patent. Specifically, the PTO addressed the question of eligibility of a patent directed to a formulation or composition which contained the active ingredient in a product approved by the FDA.

At least as applied to a patent claiming a formulation or composition, the PTO has applied an interpretation that the patent claims the approved product if it could be enforced against an infringer who was making, using, or selling the approved product. As noted by the PTO:

> If the patent could not be enforced against an infringer who was making, using or selling an ophthalmic solution containing flurbiprofen for the treatment of intraoperative miosis, it was questioned how the restoration of the lost patent term due to the regulatory process for the approved product is appropriate under the statute.

54 Fed. Reg. 30377 (July 20, 1989). On the basis of this infringement analysis, the PTO concluded that a particular patent "claimed" the product.

It is clear that the PTO has applied an infringement analysis to the question of whether a patent claims an approved product, an interpretation which is clearly consistent with the sparse legislative history on this point. Congress has twice amended § 156 following the discussion by the PTO of its interpretation of § 156(a). Thus, in Public Law 103-179, 107 Stat. 2040 (December 3, 1993), the Patent and

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Trademark Office Authorization Act of 1993, and Public Law 103-465, 1108 Stat. 4809 (December 8, 1994), the Uruguay Round Agreements Act, provisions in § 156 were made for interim patent term extensions and to provide consistency with the GATT-TRIPs agreement respectively; yet, no amendment was made to the eligibility requirements of § 156(a) in either of these legislative enactments. It is well established that when Congress revisits a statute and fails to revise or repeal the interpretation that has been expressed by the agency, it is persuasive evidence that the agency's interpretation is the one intended by Congress. *Commodity Futures Trading Comm'n. v. Schor*, 478 U.S. 833, 846 (1986) (quoting *NLRB v. Bell Aerospace Co.*, 416 U.S. 267, 274-75 (1974)).

At least ten years of past practice by the agency charged with implementing § 156 applying an infringement standard to determine whether a patent "claims" a product, and the failure of a three judge panel to obtain consensus on a single interpretation of the statutory language, would appear to evidence at least some ambiguity in the statutory language. Where the language in the statute is ambiguous, the legislative history can provide a useful tool for discerning Congressional intent.

The legislative history considered in the Hoechst-Roussel case makes plain that Congress intended the term "claims" to relate to the subject matter that the patent owner could prevent others from making, using or selling during the term of a patent. This language parallels precisely the definition of infringement in 35 U.S.C. § 271(a) as it existed at the time of enactment of § 156. Further, the legislative statement that "the first patent which claims the approved product, in the sense that the approved product

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would infringe a claim of that patent" could not be clearer. See H.R. Rep. No. 98-857 at 38, reprinted in 1984 U.S.C.C.A.N. at 2671.

In addition to this very clear statement of legislative intent, there is no discernible reason to deny patent term extension to a patent holder who could enforce the patent against an infringer during the term of the patent, and who has successfully undertaken the significant effort and cost to obtain regulatory approval. These patent holders are the intended beneficiaries of § 156. To deny patent term extension to these patent holders based on a narrow reading of the eligibility requirements of § 156(a) will seriously threaten the vitality of the incentive Congress sought to establish.

The fact that "claims" means "infringe by" is confirmed by the purpose of § 156 and the symmetry between that section and § 271(e)(1). Section 156 was intended to restore to the patent owner the term of its patent that was lost because of the requirement of regulatory approval. *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 669-671 (1990). What the patent owner loses under § 271(e)(1) is the right to sue for infringement for certain types of activity. Thus, to define "claims" more narrowly than infringement is to destroy the rights that § 156 was intended to restore.

As the Supreme Court of the United States has stated, Sections 156 and 271(e)(1) are "related parts of a single legislative package" and a symmetry exists between the benefits to patent holders of the patent term restoration provisions and the disadvantages to patent holders of the noninfringement provisions of § 271(e)(1). *Eli Lilly*, 496 U.S. at 669-72. Even though this statutory symmetry is only preferable, not

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required according to *AbTox, Inc. v. Exitron Corp.*, Appeal No. 96-1159, -1164 (Fed. Cir. August 1, 1997), it further supports a legislative intent to use an infringement test.

We believe that the PTO should continue to apply an infringement test to determine whether a patent claims a product for purposes of § 156(a). It is recognized, however, that such a view was not adopted in the Hoechst-Roussel case. Nevertheless, it is clear that the '614 patent is eligible for patent term extension under an infringement test because gemcitabine is formed in preparing the drug product GEMZAR® for administration to a patient according to the approved mode of administration by intravenous injection.

6. The decision in *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehmann* is not applicable to the facts in this application for patent term extension

The facts in this particular application are different from those addressed in the reported decision in two significant respects. First, the applicant in this case, Eli Lilly and Company, is both the patent owner responsible for the creation and development of the new product and the marketing applicant responsible for the approval of the new drug product by the FDA. Second, unlike the situation in Hoechst-Roussel, where the patent claimed a compound that was formed only after administration to a patient, the claimed compound in the '614 patent is an active ingredient present in the product when administered.

Although the majority opinion in the Hoechst-Roussel decision did not explicitly reach the issue, both the PTO and the concurring opinion by Circuit Judge Newman concluded that the patent was not eligible for patent term extension because the patent

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owner did not contribute either directly or indirectly to the marketing approval. In this case, however, Eli Lilly and Company is both the patent owner and the marketing applicant responsible for approval of GEMZAR® by the FDA. Accordingly, this basis for denial of the patent term extension application in the Hoechst-Roussel case is not applicable to the facts in this case.

Second, and most important, the patent at issue in the Hoechst-Roussel case did not claim an ingredient in the product as administered to a patient. The approved product was tacrine hydrochloride. The patent in issue claimed a chemically distinct product, 1-hydroxy-tacrine, and a method of using that product. Although tacrine hydrochloride metabolizes into another product, 1-hydroxy-tacrine, in the body of a patient after administration to a patient, the compound falling within the scope of the Hoechst patent claims was not present in the product as administered to the patient. In the present case, by contrast, gemcitabine is present as an active ingredient in the product when administered to a patient. This is a significant distinction because the Court in *Glaxo* held that an "ingredient" must be present in the drug product when administered to be eligible for patent term extension under § 156. Accordingly, the present facts are clearly distinguished from the facts which lead the Court in Hoechst-Roussel to deny eligibility for patent term extension under § 156.

For all the reasons advanced above, it is respectfully submitted that U.S. Patent 4,808,614 is eligible for patent term extension under 35 U.S.C. § 156. Favorable

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reconsideration of the decision dismissing the application for patent term extension is requested.

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